CASE REPORT

Intestinal granulomatous disease: what is the first call

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SUMMARY

A 15-year-old girl presented with erythema nodosum and mild abdominal complaints. Her intestinal granulomatous disease was erroneously diagnosed as Crohn's disease despite the fact that the possibility of tuberculosis was considered. The final diagnosis of tuberculosis was made only when an anti-tumour necrosis factor therapy resulted in further deterioration. The patient was treated with isoniazid, rifampin, pyrazinamide and ethambutol, with slow and steady clinical improvement until complete recovery was achieved.

BACKGROUND

In 2015, 1.8 million people worldwide died from tuberculosis (TB).¹ Israel, a country with low TB rates, has absorbed approximately 900 000 new immigrants in the last three decades, mainly from TB endemic countries (the former Soviet Union Republics and Ethiopia). Eighty-five per cent of all new TB cases occur in people born outside Israel, and 65% of new cases are those of recently arrived immigrants.² TB rates more than doubled from 4.2/100 000 in 1987 to 10.2/100 000 in 1991 and remained relatively high (6–8/100 000) in the last decade of the 20th century.³ In the European Union surveillance report, extrapulmonary manifestations were encountered in 22.4% of all notified cases of TB in 2011.⁴ In this report, genitourinary and gastrointestinal cases were responsible for 6.9% and 2.7% of total extrapulmonary manifestations, respectively.⁴ The differential diagnosis of enteric disease differs between developed countries, where inflammatory bowel disease (IBD) predominates, and low-income/middle-income countries, where enteric infections prevail. This classification is blurred in immigration-absorbing countries such as Israel. This case demonstrates these differences in the epidemiology of intestinal granulomatous disease and illustrates the major difficulties of the correct diagnosis.

CASE PRESENTATION

A 15-year-old Ethiopian-born girl presented with erythema nodosum and vague abdominal pain without any additional complaints. The girl was the eldest of seven children in a family of immigrants who lived together. Soon after immigrating to Israel, 3 years before presentation she had been treated with isoniazid for 9 months following a positive tuberculin skin test. Her medical history was otherwise unremarkable. She had low stature

(147 cm, <3 percentile) with a BMI of 17.8 kg/m² on presentation, but no previous data regarding her growth were available.

INVESTIGATIONS

Laboratory tests revealed haemoglobin of 9.8 g/dL, mean corpuscular volume (MCV) of 63 fL, erythrocyte sedimentation ratio (ESR) of 103 mm/hour, C-reactive protein (CRP) of 38 mg/L and albumin of 3.3 g/dL, and HIV test was negative. An upper gastrointestinal series showed irregularity and ulcerations of the duodenal wall. Endoscopic studies demonstrated severe duodenal and ileal inflammation with ulcerations and a cobblestone appearance of the mucosa. Biopsies revealed inflammation with granulomas, negative for acid-fast bacilli. Her chest X-ray was normal and cultures of gastric aspirate and urine did not grow *Mycobacterium tuberculosis* (Mtb).

DIFFERENTIAL DIAGNOSES

Except IBD and enteric TB, the differential diagnoses of intestinal granulomatous inflammation diseases include other enteric infections like *Yersinia*, and other inflammatory conditions such as intestinal sarcoidosis and Behcet's disease.^{5 6}

TREATMENT

A diagnosis of Crohn's disease (CD) was made. Steroids (oral prednisolone 1 mg/kg/day) and 6-mercaptopurine (1 mg/kg/day) therapy were started. Clinical improvement was noted, with resolution of her main symptoms with normalisation in the level of inflammatory markers. The steroid therapy had been tapered down but was not stopped. After several months of an indolent course, the disease relapsed with painful leg nodules and abdominal pain, which was interpreted as failure of steroid treatment; therefore, infliximab (7.5 mg/kg per dose every 4 weeks) was prescribed.

Four months later, after three doses of infliximab, bilateral leg oedema developed. White cell count was $1.87 \times 10^9/L$, ESR was 49 mm/hour, CRP was 44 mg/L, and albumin had decreased to 2.8 g/dL. An abdominal CT examination revealed severe intestinal disease, enlarged retroperitoneal lymph nodes with central low attenuation, pressure on the inferior vena cava, bilateral psoas abscesses and bilateral hydronephrosis. In addition, calyceal erosions in the left renal collecting system, calcifications of the ovaries and cholelithiasis were demonstrated

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Figure 1 A coronal CT image demonstrates multiple low-attenuation lymph nodes in the retroperitoneum (arrows). ao, aorta; IVC, inferior vena cava; LK, left kidney.

(figures 1 and 2). A percutaneous CT-guided biopsy of a retroperitoneal lymph node yielded necrotising granulomas. Ziehl-Neelsen stain and culture for *Mtb* were negative.

OUTCOME AND FOLLOW-UP

TB was diagnosed based on the presence of 'cold abscesses' with granuloma formation and radiological evidence of lymph node and genitourinary tract involvement, which are typical of TB rather than CD.⁷ She was treated with isoniazid, rifampin, pyrazinamide and ethambutol, with slow and steady clinical improvement.

DISCUSSION

Misdiagnosis of CD and intestinal TB (ITB) is common; both diseases usually start insidiously and can go undiagnosed for many years. However, the presentation of perforation and abscess complicating CD is usually of an acute disease accompanied by marked inflammatory reaction. Abscess formation in TB is usually insidious with minimal inflammatory symptoms and signs, often referred as 'cold abscesses'.⁸

Endoscopy with biopsies can distinguish between the two conditions only to a certain extent, and the classic pathological features of ITB, caseating granulomas with acid-fast bacilli, are present in less than 30% of cases.^{6,9}

Diagnosis of ITB through positive culture is an exception reported in less than 30% of cases.¹⁰ In the European Union surveillance report, only 33.7% of the cases of extrapulmonary

Figure 2 A coronal maximum intensity projection image shows bilateral hydronephrosis. In the left kidney there are calyceal erosions (arrow), as well as a thick-walled ureter.

TB had their diagnosis confirmed by culture.⁴ In our case, only one sample for *Mtb* culture was taken when ITB progressed.

The main differential diagnoses, IBD and ITB, require different, even opposing, therapeutic approaches: immunosuppressive therapy for IBD or antituberculous therapy with four drugs.

Administration of corticosteroids has been shown to ameliorate the inflammation during TB infection by downregulation of proinflammatory cytokines.¹¹ Corticosteroids have been tested as an adjunct to standard antibiotic therapy in various forms of TB.¹² A primary remission in response to an empirical course of corticosteroids or other immunosuppressive agents is not specific and can occur in both ITB and CD.¹³ On the contrary,

Learning points

- ▶ Misdiagnosis of Crohn's disease and ITB is common; both diseases usually start insidiously and can go undiagnosed for many years.
- ▶ Patients with intestinal granulomatous disease who have emigrated from countries with a high prevalence of tuberculosis should be first investigated for active tuberculosis.
- ▶ In some cases when the diagnosis of intestinal granulomatous disease remains elusive, empirical antituberculous therapy is justified.

the response to antituberculous therapy is specific and would further support this diagnosis with extension of the treatment course to 6–9 months. CT study may reveal involvement of lymph nodes, omentum and the genitourinary tract, all of which are much more typical of ITB than CD,⁷ and enable biopsy and culture. When only gut involvement is encountered, submission of several biopsy specimens for culture and PCR for mycobacteria is mandatory to improve the diagnostic yield of ITB or to allow its reliable exclusion prior to immunosuppressive therapy.

If the odds for both are equal, empirical therapy for ITB first is justified, as can be inferred from the words of Crohn *et al*,¹⁴ who suggested surgery for regional enteritis only after ‘accepted methods of treatment for tuberculosis had been exhausted’.¹⁴

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